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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,036	10/02/2003	John A. Mikszta	P-6088	1666

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EXAMINER
MCGAW, MICHAEL M

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/679,036	**Applicant(s)** MIKSZTA ET AL.
	Examiner Michael M. McGaw	**Art Unit** 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2004*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-15* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Oath/Declaration

It is noted that the declaration lists one of the inventors as Monath P. Thomas. Does applicant wish to change this to Thomas P. Monath?

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-12 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 indicates that the virus is being delivered via abrasion. On initial reading this seems reasonably clear. However, dependent claim 9 would indicate that the vaccine is delivered via at least one microneedle. So then the question becomes, what is meant by the term "a device that abrades an epidermal layer of the skin's surface while delivering the chimeric virus"? The specification does not satisfactorily answer this question. The specification indicates that "the invention encompasses any method known method in the art for delivering a vaccine to the epidermal compartment of a subject's skin…" which would not exclude a traditional needle. (See p. 15, paragraph 0047). It seems that a needle could cause a form of microabrasion upon entry at the site of inoculation. Is that what applicant is indicating in claim 9? Does microabrasion exclude injection? What about delivery via a gun that forces particles into the skin using gas? Certainly such particles "abrade" the superficial layer on top. After considering all the claims, it becomes unclear what is encompassed by a “device that abrades.” Therefore, the claims are rendered indefinite.

Claim Rejections - 35 USC § 112, ¶1

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for either Japanese encephalitis virus or Dengue virus, does not reasonably provide enablement for all flaviruses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification teaches chimeric constructs using either dengue virus envelope protein or Japanese encephalitis virus envelope protein. It is not clear that one could necessarily construct a chimeric yellow fever virus expressing an envelope protein of other flaviviruses. For instance, one could imagine replacing the coding region of the envelope protein of YF 17D with that of hepatitis C virus envelope protein. One cannot say apriori that such a construct could produce chimeric virus. Chambers, et al (1999), discussed more fully below, indicates that there is some difficulty in generating such constructs where the envelope protein of YF17D is exchanged for homologous envelope sequences, especially where the capsid sequence is supplied by the non-YF17D virus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 3-6, 10-11 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,696,281 B1 to Chambers et al.

Applicant claims "[a] method for inducing an immune response to a flavivirus viral antigen in a subject, comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivrus virus to a subject's skin using a device that abrades an epidermal layer of the skin's surface while delivering the chimeric virus."

U.S. Patent No. 6,696,281 B1 ('281) teaches chimeric flavivrus vaccines using YF as the backbone into which the gene for the prM-E protein of another flavivrus is inserted. The '281 patent is primarily directed at a tetravalent vaccine for dengue virus infection. The '281 patent indicates that it is to be administered by "intramuscular, subcutaneous, or intradermal routes."(col. 81, line 9) Thus, it appears to contemplate the delivery of such a vaccine to the epidermis of a vaccinee. While not mentioned explicitly, it is implicit that the vaccine must be delivered by some means to the epidermal compartment. The first vehicle to come to mind for such a delivery would be a traditional syringe and needle. It would seem that the displacement of the overlying skin caused by the entry of a needle could be a form of abrasion. Devices such as the

PowderJect or a specialized needle and syringe (See for instance US Pat. No. 6,569,143 B2 teaching intradermal delivery devices suitable to deliver YF vaccine; col. 15, line 16) would also work, while causing this form of abrasion. Thus, it is asserted that the '281 patent anticipates claims 1, 3-6, 10-11 and 15 of the present application.

Claims 11 and 15 are rejected under 35 U.S.C. 102(b) as being anticpated by Guirakhoo, F. et. al.

Claim 11 is directed to a kit for use in inducing an immune response to a flavivirus antigen using chimeric YF virus expressing the envelope gene product of a flavivirus and a device that abrades an epidermal layer while delivering the virus.

Guirakhoo, F. et. al. (2000) J. Virol. 74(12) pp. 5477-5485 teach compositions for inducing an immune response to a flavivirus viral antigen in a subject, comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivrus virus. Guirakhoo, F. et. al. is discussed more fully below. It would seem that the displacement of the overlying skin caused by the entry of a needle could be a form of abrasion. Furthermore, the claim says nothing about the compartment to which the vaccine is delivered. Consequently, Guirakhoo, F. et. al. appears to anticipate claims 11 and 15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guirakhoo et al (2000) in view of Wu et al. (2000).

Applicant claims "[a] method for inducing an immune response to a flavivirus viral antigen in a subject, comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivrus virus to a subject's skin using a device that abrades an epidermal layer of the skin's surface while delivering the chimeric virus."

Guirakhoo, F. et. al. (2000) J. Virol. 74(12) pp. 5477-5485 teach a method for inducing an immune response to a flavivirus viral antigen in a subject, comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivrus virus. Guirakhoo et. al. utilized a construct identified as ChimeriVax-D2. (p. 5478, col. 1) This construct used the YF vaccine strain 17D cDNA as a backbone into which the premembrane and envelope genes of dengue-2 virus (PUO-218 strain) was switched for the corresponding YF genes. Guirakhoo et. al. showed that monkeys receiving the vaccine were protected against challenge with a wild-type dengue virus, whereas monkeys receiving only YF17D or no vaccine at all became viremic upon challenge. (see pg. 5484, col. 1 and table 9). Animals were immunized via the subcutaneous route. (p. 5478, col. 1). Guirakhoo et. al. do not teach delivering the vaccine to a subject's skin using a device that abrades an epidermal layer of the skin's surface while delivering the chimeric virus.

Wu, et. al. (2000) *Nature Medicine* 6(7) pp. 816-820 teach that human skin Langerhans cells are targets of dengue virus infection. Wu, et. al. exposed human skin

DCs (Langehans cells and dermal/interstitial dendritic cells) to dengue virus (DV) *ex vivo* and found that, of the emigrants from the dermis and epidermis, 60-80% expressed DV antigen. (see abstract) These results were supported by histologic examination from the skin rash of a human volunteer who had received a live attenuated tetravalent DV vaccine. (pg. 818) Langehans cells and dermal/interstitial dendritic cells are known to important immune cells localized within the skin of humans. Wu, et. al. concludes that human skin DCs are permissive for DV infection , and provide a potential mechanism for the transmission of DV into human skin. US. Patent No. 6,589,531 B1 is cited as evidence that one working with a chimeric YFV vaccine would recognize that such a vaccine should be administered by "routes which mimic the route by which the infection by the pathogen of interest occurs." (See col. 10, line 30) This includes administration via the intradermal route. (col. 10, line 39) The point being that one working with such a vaccine would want to deliver the vaccine via the intradermal route because (1) this is the site at which dengue virus is deposited in the saliva of a mosquito during blood-feeding activity and (2) Wu, et. al. shows that the Langerhans cells are the targets of Dengue virus infection. One of ordinary skill in the art would recognize that displacement of the superficial epithelial portion is required to deliver the vaccine to the underlying skin. It would seem that a needle would displace the top layer in manner that could be considered a microabrasion to delver the vaccine to the underlying intrermal/epidermal space. Others have utilized specialized delivery systems to by-pass the top layer of skin to reach the underlying viable epidermis. For instance, Chen, D. et al. (2000) Nature Medicine 6(10) 1187-1190 teaches epidermal immunization by a needle-free powder delivery system to deliver influenza vaccine. Chen points out that "Human vaccines are typically injected into muscle despite its inconsequential function in the induction of subsequent immune responses." Skin, on the other hand, is a potent immunological induction site that can be very efficacious. (see p. 1187, col. 1).

One of ordinary skill in the art would have been motivated to administer the chimeric yellow fever vaccine because it is recognized that the skin is the route of entry and the target of infection for many flavivuses as shown by Wu, et. al. One of ordinary skill in the art would have expected to have achieved an enhanced method of inducing an immune response using a chmeric YF virus vaccine because Guirakhoo, F. et. al. teach the efficacy of chimeric YF virus vaccines expressing an envelope gene product of a flavivirus while Wu, et. al. teaches that the Langerhan cells and dermal/interstitial DCs are the targets of infection. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guirakhoo et al (2000) in view of Wu et al. (2000) as applied to claims 1, and 3-15 above, and further in view of Chambers, et al. (1999).

Claim 2 specifies that the flavivirus is Japanese encephalitis (JE) virus. Guirakhoo et al (2000) in view of Wu et al. (2000) do not teach JE virus.

Monath, et al. (2000) J. Virol. 74(4) pp. 1742-1751 teach a method for inducing an immune response to a flavivirus viral antigen in a subject, comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivrus virus.

Monath, et al. utilized a YF17D-JE construct termed ChimeriVax-JE. (p. 1743) This construct used the YF vaccine strain 17D cDNA as a backbone into which the premembrane and envelope genes of JE was switched for the corresponding YF genes. JE virus. Monath indicates that immunized monkeys were protected from i.c. challenge from JE virus. (p. 1744) Importantly, Monath indicates that "a small amount of virus injected by a mosquito and sterilized by preexisting antibody in the host can generate a boost in immunity." (see p. 1749, col. 1) This contemplates that the typical route of infection is in the skin. Furthermore, this indicates that delivery to the skin is sufficient to raise an immune response.

One of ordinary skill in the art would have been motivated to administer the chimeric yellow fever vaccine because it is recognized that the skin is the route of entry and the target of infection for many flavivuses as shown by Wu, et. al. Monath further shows that mosquito saliva containing virus boosts the response further implicating the id route of delivery. One of ordinary skill in the art would have expected to have achieved an enhanced method of inducing an immune response using a chmeric YF virus vaccine because Monath, F. et. al. teach the efficacy of chimeric YF virus vaccines expressing an envelope gene product of a flavivirus. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571)

272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Wednesday, September 29, 2004

Mary Mosher

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600